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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| EXAMINER | |
|---|---|
| HAMA, JOANNE | |
| **ART UNIT** | **PAPER NUMBER** |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/573,212 | AKIRA ET AL. | |
| | Examiner | Art Unit | |
| | Joanne Hama, Ph.D. | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) *4-5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

This Application, filed September 21, 2006, is a 371 of PCT/JP04/14220, filed September 29, 2004 and claims priority to foreign application, 2003-338013, filed September 29, 2003, in Japan.

Claims 1-5 are under consideration.

Claims 4, 5 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiply dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

### *Information Disclosure Statement*

Applicant filed an Information Disclosure Statement (IDS) March 26, 2006. The IDS has been considered.

### *Priority*

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-3 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial utility or a well established utility. According to the Revised Utility Examination Guidelines, see the Federal Register, Vol. 66, No. 4, pp. 19092-1099 (January 5, 2001), also available at http://uspto.gov/web.menu.utility.pdf, the following definitions of credible, specific, and substantial apply.

A credible utility is one that a person of ordinary skill in the art would accept as currently available. An assertion is considered credible unless (a) the logic underlying the assertion is seriously flawed, or (b) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the Applicant to support the assertion of utility. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use.

A specific utility is one that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention.

A substantial utility is one that defines a real world use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a real world context of use are not substantial utilities. Research that involves studying the properties of the claimed product itself does not constitute a substantial utility.

See also MPEP 2107-2107.02, and *Brenner, Comr. Pats. v. Manson*, 148 USPQ 689 (US SupCt 1966).

The instant claims are drawn to a non-human animal comprising a disruption in its TRAM gene, wherein the non-human animal exhibits a non-responsiveness to endotoxin. The specification identifies the following uses for the claimed mice: 1) the use of the non-human animals or cells derived from the non-human animal to evaluate the role of the TRAM gene 2) the use of the non-human animals or cells derived therefrom to identify substances that promote or suppress the responses to TLR4 ligands (specification, page 14, 3rd parag. to page 15, 1st parag.). The claims also encompass heterozygous and chimeric non-human animals. The specification does not provide any particular use for these non-human animals other than their use to make non-human animals comprising a homozygous disruption in TRAM. As such, the use of these non-human animals depend on the utility of the homozygous TRAM disrupted non-human animals.

In regards to asserted utility 1), as identified above, the stated utility of the non-human animal for evaluating the role of the TRAM gene or gene product or for defining disease pathways associated with the TRAM gene or gene product does not constitute a real world utility and therefore is not a substantial utility, but rather represents further research on the product to identify or reasonably confirm a real world utility. As stated in the Guidelines set forth above, research that involves studying the properties of the claimed product itself does not constitute a substantial utility. Further, such an asserted utility constitutes a general, rather than a specific utility, as all knockout non-human

animals can be used to study the effects of the loss of function of the gene that is disrupted. Therefore, asserted utility 1) does not meet the standard for a specific and substantial utility.

In regards to asserted utility 2), as identified above, the specification fails to demonstrate that mice with a homozygous disruption of an endogenous TRAM gene have any phenotype associated with any disease, or can in fact be used as a model for any particular disease. Further, while the specification contemplates that the claimed homozygous non-human animals could be used to screen for substances that promote or suppress the response to ligands recognized by TLR4, and those promoting substances can be used as preventive/treating agents for bacterial infections (specification, page 16 3rd parag. to page 17, 1st parag.), the specification does not teach what distinguishes the claimed non-human animals from wild type non-human animals in screens for medicaments that prevent or treat bacterial infections. For further discussion, see Enablement. As such, asserted utility 2) is not readily apparent.

Thus, in view of the discussion above, the skilled artisan would not find any of the asserted utilities of the non-human animals to be specific and substantial, or well-established.

Claims 1-3 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 1-3 encompass non-human animals wherein the mutation occurs naturally and are a product of nature. This is non-statutory

subject matter. Use of the word, "transgenic" to describe the non-human animals in claims 1-3 would be remedial.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the

presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claims are drawn to a non-human animal comprising a disruption in its endogenous TRAM gene, wherein the non-human animal exhibits non-responsiveness to endotoxin.

As discussed above, the use of the claimed non-human animal in screens for substances that promote the response to ligands recognized by TLR4, such that these substances can possibly be used as preventive/treating agents for bacterial infections is not readily apparent. The claimed non-human animals are non-responsive to endotoxin and it is inferred from this phenotype that they do not exhibit symptoms related to the presence of endotoxin, such as endotoxic shock, see for example, Wanecek et al., 2000, European Journal of Pharmacology, 407: 1-15. This means that the claimed non-human animals do not exhibit any phenotype related to any disease or disorder and thus, the use of the claimed non-human animals for reasons other than as a model of disease is not readily apparent. In addition to this issue, while the specification indicates that the claimed non-human animals can be used in screens for substances that promote the response to ligands recognized by LTR4, such that the substances can possibly be used in prevention or treatment of bacterial infections, nothing in the specification indicates what phenotype the claimed non-human animals have over that

of wild type animals, such that the screen for substances that prevent or treat bacterial infections requires the use of them.

In addition to this issue, the art at the time of filing teaches that an artisan cannot readily predict that knockout mice or any non-human knockout animals exhibiting phenotypes are readily usable as models of any human disease or disorder. The discussion regarding this issue is as follows.

At the time of filing, the art did not consider the phenotype of a knockout or transgenic mouse to be predictable. In addition, the art did not consider the correlation between any observed mouse phenotypes and human disease phenotypes as predictable. Doetschmann teaches that "[o]ne often hears the comment that genetically engineered mice, especially knockout mice, are not useful because they frequently do not yield the expected phenotype, or they don't seem to have any phenotype" (Doetschmann, 1999, Lab. Animal Sci., 49: 137-143, see page 137, column 1, paragraph 1). Doetschmann provides numerous examples of instances in which genes considered well-characterized *in vitro* have produced unexpected phenotypes or indiscernible or no phenotypes in transgenic or knockout mice. Moens et al. further teaches that different mutations in the same gene can lead to unexpected differences in the phenotype observed. Moens et al. shows that two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse embryonic stem cells, one leaky and one null (Moens et al., 1993, Development, 119: 485-499). Further, the art demonstrates the unpredictability of making a mouse model for human disease by disrupting the murine

gene. Jacks et al. teaches that although retinoblastoma (Rb) gene mutations in humans are associated with retinal tumors, Rb gene knockout mice had tumors in the pituitary gland rather than the retinas (Jacks et al., 1992, Nature, 359: 295-300). Likewise, whereas HPRT deficiency in humans is associated with Lesch-Nyhan syndrome, a severe neurological disorder, HPRT-deficient mice are phenotypically normal (Kuehn et al., 1987, Nature, 326: 295-298 and Jaenisch, 1988, Science, 240: 1468-1474). In another case of the art teaching that the correlation between any observed mouse phenotype and human disease phenotypes as predictable, Racay, 2002, Bratisl Lek Listy, 103: 121-126, teaches that:

> "mutations of some genes led to phenotype showing severe defects, which did not correspond to any clinically important disorder, indicating either high *in vivo* stability of the gene or the interspecies differences. From the view of human medicine, the differences among the species (it means the differences in genetic background, gene expression, metabolism, and signal transduction) represent the main limitation of the use of genetically modified animals as models of human diseases. Therefore some results acquired by this approach can not be applied in human medicine because of the differences between rodents and human beings (Racay, page 124, under point 5)."

Thus, the art at the time of filing clearly establishes the unpredictability of determining the phenotype of transgenic or knockout mouse even when the activity of the gene has been extensively studied *in vitro*, and further establishes the unpredictability of generating a mouse model for human disease based on the activity of the gene in humans.

In addition to this issue, Jakel et al., 2004, Nature Reviews: Genetics, 5: 136-144 provides examples of transgenic mice wherein species-specific differences causes

problems in generating a human model of disease. In the case of making the Huntington's disease model, Jakel et al. teach that part of the difficulty in making a mouse model likely stems from the species differences of mouse and humans. These species differences include a rodent's basal ganglia is less vulnerable than its human counterpart, and that basic cellular biology, such as post-translational modification, is different from humans (Jakel et al., page 137, 2nd col., 3rd parag.). As these issues apply to the instant invention, an artisan cannot predict what phenotypes a knockout mouse will exhibit, nor can an artisan predict that knockout mice are necessarily models of a disease or disorder.

Coupled with the fact that phenotypes are unpredictable in knockout mice, the art teaches that non-specific effects, such as genetic background of the animal can cause non-specific phenotypes to be exhibited. At the time of filing, the art teaches that while the promise of gene targeting had been to reveal the *in vivo* function of a gene of interest, the functional relevance of gene targeting has been questioned because the mutation might lead to an avalanche of compensatory processes (up- or downregulation of gene products) and resulting secondary phenotypical changes. Thus, a null mutant organism might not only lack the produce of a single gene, but might also possess a number of developmental, physiological, or even behavioral process that have been altered to compensate for the effect of the null mutation (Gerlai, 1996, Trends Neurosci, 19: 177-181, page 177, 1st col., 1st parag.). Gerlai teaches an example wherein background genotype can confound the exhibited phenotypes. Targeted disruption of a gene of interest, $\alpha$, might lead to changes in expression of alleles b and B for gene $\beta$. A

regulatory change in gene β might lead to different phenotypic changes, depending on which allele (b or B) is present in the organism with the null mutation in gene α. The upshot of this problem is that due to this polymorphism in the genetic background, one cannot conclude for certain that a phenotypic change exhibited in a null-mutant mouse resulted from the null mutation or to the genetic background (Gerlai, page 177, 1st col., under "Polymorphism in the genetic background might make the results of gene-targeting studies difficult to interpret"; see also Pearson, 2002, Nature, 415: 8-9; page 8, 1st col., 5th parag.). With respect to the instant invention, Gerlai's teachings indicate that even if an artisan were to identify a phenotype in the claimed mice, an artisan would need to carry out experimentation to determine whether the phenotype was related to the TRAM gene or was a result of a non-specific interaction with the disrupted gene. An artisan would also need to determine whether the phenotype was related to any disease or disorder. This is undue experimentation because nothing in the art or specification at the time of filing teaches any relationship between the gene, a disease or disorder, and phenotypes associated with the disease or disorder.

The claims broadly encompass the use of ES cells from any species of non-human animal. such that any non-human animal comprising a disruption in TRAM is obtained. At the time of filing, the art teaches that the only known non-human animal in which ES cells can be obtained and be used to make knockout animals was mouse. This is because mice are the only mammals in which ES cells can be generated and which chimerism from ES cells extend to the germline (Murray, et al., 1999, *Transgenic Animals in Agriculture*, CAB International: Oxon, pages 58-61, page 60 2nd parag.; see

also Denning and Priddle, 2003, Reproduction, 126: 1-11, who teach that the only known species of ES cells that transmit to the germline is mouse, Denning and Priddle, page 2, 2nd col., 1st parag. under "The need for nuclear transfer"). As the teachings of Murray et al. and Denning and Priddle apply to the instant invention, while the specification and the art teach how to make transgenic mice with ES cells, neither the specification nor the art teaches how to obtain ES cells from other species of animals such that an artisan can obtain a line of transgenic non-human animals comprising the transgene of interest. Thus, while the specification and the art teach transgenic mice, the specification and the art do not provide guidance for the full breadth of the claims.

Therefore, in view of the art recognized unpredictability in determining the phenotype of transgenic or knockout non-human animal even when the activity of the gene has been extensively studied *in vitro*, and the unpredictability of generating a non-human animal model for human disease based on the activity of the gene in humans, the unpredictability in correlating any observed phenotype in a knockout non-human animal with gene disruption as acknowledged by both the prior art and the specification, and the breadth of the claims as written, it would have required undue experimentation to practice the instant invention as claimed.

***Conclusion***

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Joanne Hama
Art Unit 1632